C60

ISENBRUCK | BÖSL | HÖRSCHLER | WICHMANN | HUHN
Patentanwälte

Patentanwälte, Postfach 860 880, D-81635 München

European Patent Office

80298 München (DE)

Dr. Raphael Bösl
Postfach 860 880
81635 München

Tel. +49 (89) 99 88 54-0
Fax +49 (89) 99 88 54-99
boesl@ib-patent.de

Munich,
Mai 28, 2003

Patentanwälte & European Patent and Trademark Attorneys

MANNHEIM

Günter ISENBRUCK
Dr.phil.nat. - Dipl.-Chem.

Wolfram HÖRSCHLER
Dipl.-Ing.

Alexander SCHUCK
Dr.rer.nat. - Dipl.-Chem.

Hedwig KERN
Dr.rer.nat. - Dipl.-Ing.

MÜNCHEN

Raphael BÖSL
Dr. rer. nat. - Dipl.-Chem.

Hendrik WICHMANN
Dr. rer. nat. - Dipl.-Biol.

Fritz LAHRTZ
Dr. rer. nat. - Dipl.-Natw. ETH

Richard RÖDER[1]
Dr. rer. nat. - Dipl.-Biol.

HEIDELBERG

Michael HUHN
Dr.rer.nat. - Dipl.-Chem.

DÜSSELDORF

Stefan FÉAUX DE LACROIX
Dr.rer.nat. - Dipl.-Chem.

Dorothee HOLLAH
Dr.rer.nat. - Dipl.-Chem.

[1]*Patentanwälte*

Opposition to	EP 1 144 623 B1 (00910510.7)
Proprietor	Ribopharma AG (DE)
Opponent:	Aventis Pharma Deutschland GmbH (DE)
Our Ref:	A62245EP BÖ/Röd

Notice of Opposition

In the name of and on behalf of

Aventis Pharma Deutschland GmbH
65929 Frankfurt am Main (DE)

I herewith file an opposition against the European patent EP 1 144 623 B1 (00910510.7) with the title: "Verfahren und Medikament zur Hemmung der Expression eines vorgegebenen Gens (Method and Medicament for Inhibiting the Expression of a Defined Gene).

Proprietor of the patent:

Ribopharma AG
Universitätsstraße 30
95440 Bayreuth (DE)

Zur Kasse

The opposition fee of EUR 610,- shall be debited from the deposit account No. 28001211.

1. Requests

1.1 Opposition is filed against the European patent EP 1 144 623 B1 as a whole.

1.2 In alternative, oral proceedings according to Art. 116 EPC are requested.

2. Grounds for Opposition

Opposition is based on all grounds mentioned in Article 100(a), (b) and (c) EPC:

2.1 The subject-matter of the opposed European patent extends beyond the content of the application as filed, and therefore violates Article 123(2) EPC.

2.2 Further, the subject-matter of the opposed European patent is not patentable within the terms of Articles 54 and 56 EPC.

2.3 Further, the opposed European patent does not disclose the alleged invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and therefore violates Article 83 EPC.

3. Cited Prior Art

The opposition is based on the following documents, which shall be cited in the proceedings with the numbering indicated below:

D1: Rosalind C. Lee, Rhonda L. Feinbaum, and Victor Ambros, The C. elegans Heterochronic Gene lin-4 Encodes Small RNAs with Antisense Complementarity to lin-14, Cell, Vol. 75, 843-854, December 3, 1993

Enclosure D1

D2: Eric G. Moss, Rosalind C. Lee, and Victor Ambros, The Cold Shock Domain Protein LIN-28 Controls Developmental Timing in C. elegans and Is Regulated by the lin-4 RNA, Cell, Vol. 88, March 7, 1997, 637-646

Enclosure D2

D3: Andrew Fire, SiQun Xu, Mary K. Montgomery, Steven A. Kostas, Samuel E. Driver & Craig C. Mello, Potent and specific genetic interference by double-

stranded RNA in Caenorhabditis elegans, Nature, Vol 391, 19 February 1998, 806-8113

Enclosure D3

D4: Yang Shi, and Craig Mello, A CBP/p300 homolog specifies multiple different pathways in Caenorhabditis elegans, Genes & Development Vol. 12, No. 7, pp. 943-955, April 1, 1998

Enclosure D4

D5: Mary K. Montgomery and Andrew Fire, Double-stranded RNA as a mediator in sequence-specific genetic silencing and co-suppression, TIG July 1998, Vol. 14, No. 7, 255- 258

Enclosure D5

D6: Peter M. Waterhouse, Michael W. Graham, and Ming-Bo Wang, Virus resistance and gene silencing in plants can be induced by simultaneous expression of sense and antisense RNA, Proc. Natl. Acad. Sci. USA, Vol. 95, Issue 23, 13959-13964, November 10, 1998

Enclosure D6

D7: Mary K. Montgomery, SiQun Xu, and Andrew Fire, RNA as a target of double-stranded RNA-mediated genetic interference in Caenorhabditis elegans, Proc. Natl. Acad. Sci. USA, Vol. 95, pp. 15502-15507, December 1998

Enclosure D7

D8: Jason R. Kennerdell and Richard W. Carthew, Use of dsRNA-mediated Genetic Interference to Demonstrate that frizzled and frizzled 2 Act in the Wingless Pathway, Cell, Vol. 95, 1017-1026, December 23, 1998

Enclosure D8

D9: Phillip A. Sharp, RNAi and double-stranded RNA, Genes & Development Vol. 13, No. 2, pp. 139-141, January 15, 1999

Enclosure D9

D10: Lisa Timmons and Andrew Fire, 1998 October 29, Specific interference by ingested dsRNA, Nature 395(6705):854

Enclosure D10

D11: WO 99/32619, Priority Data: December 23, 1997 US 60/068,562, December 18, 1998 US 09/215,257; International Publication Date July 1, 1999

Enclosure D11

D12: Anna Wargelius, Ståle Ellingsen, Anders Fjose, Double-Stranded RNA Induces Specific Developmental Defects in Zebrafish Embryos, Biochemical and Biophysical Research Communications 263, 156-161, September 16, 1999

Enclosure D12

D13: Andrew Fire, RNA-triggered gene silencing, TIG September 1999, volume 15, No. 9, 358-363

Enclosure D13

D14: Andrew J. Hamilton and David C. Baulcombe, A Species of Small Antisense RNA in Posttranscriptional Gene Silencing in Plants, Science, Vol. 286, 29 October 1999, 950-951

Enclosure D14

D15: WO 99/61631, Priority Data: May 26, 1998 US 09/084,942; International Publication Date December 2, 1999

Enclosure D15

D16: Tuschl T, Zamore PD, Lehmann R, Bartel DP, Sharp PA, Targeted mRNA degradation by double-stranded RNA in vitro, Genes & Development 1999 Dec 15;13(24):3191-7

Enclosure D16

D17: Phillip D. Zamore, Thomas Tuscl, Phillip Sharp, and David P. Bartel, RNAi: Double-Stranded RNA Directs the ATP-Dependent Cleavage of mRNA at 21 to 23 Nucleotide Intervals, Cell, Vol. 101, 25-33, March 31, 2000

Enclosure D17

D18: Dr. Angelika Fallert-Müller, Lexikon der Biochemie, Spektrum Verlag 2000, Band 2, S. 448-449

Enclosure D18

4. Subject-Matter of the Contested European Patent EP 1 144 623 B1

According to the independent claims the alleged invention refers to:

1. A method for inhibiting the expression of a given target gene,
2. in a cell,
3. in vitro,
4. where an oligoribonucleotide is introduced into the cell,

5. the oligoribunocleotide has a double-stranded structure (dsRNA),
6. the dsRNA is formed by two separate RNA single strands,
7. one strand of the dsRNA has a region which is complementary to the target gene,
8. the compelementary region has less than 25 successive nucleotide pairs.

Claim 1

1. A medicament with at least one oligoribonucleotide,
2. the oligoribunocleotide has a double-stranded structure (dsRNA),
3. the dsRNA is formed by two separate RNA single strands,
4. the oligoribonucleotide is for inhibiting the expression of a given target gene,
5. one strand of the dsRNA has a region which is complementary to the target gene,
6. the compelementary region has less than 25 successive nucleotide pairs.

Independent Claim 32

1. An active ingredient with at least one oligoribonucleotide,
2. the oligoribunocleotide has a double-stranded structure (dsRNA),
3. the dsRNA is formed by two separate RNA single strands,
4. the oligoribonucleotide is for inhibiting the expression of a given target gene
5. one strand of the dsRNA has a region which is complementary to the target gene,
6. the target gene is part of a phytopathogenic virus or viroid,
7. the complementary region has less than 25 successive nucleotide pairs.

Independent Claim 63

1. Use of an oligoribonucleotide for preparing a medicament or active ingredient for inhibiting the expression of a given target gene,
2. the oligoribonucleotide has a double-stranded structure (dsRNA),
3. the dsRNA is formed by two separate RNA single strands,
4. one strand of the dsRNA has a region which is complementary to the target gene,

5. the compelementary region has less than 25 successive nucleotide pairs.

Independent Claim 81

1. Use of a vector for coding at least one oligoribonucleotide,
2. the oligoribonucleotide is for preparing a medicament or active ingredient,
3. the oligoribonucleotide has a double-stranded structure (dsRNA),
4. the dsRNA is formed by two separate RNA single strands,
5. the oligoribonucleotide is for inhibiting the expression of a given target gene,
6. one strand of the dsRNA has a region which is complementary to the target gene,
7. the complementary region has less than 25 successive nucleotide pairs.

Independent Claim 114

For the subject-matter of dependent claims 2 to 31, 33 to 62, 64 to 80, 82 to 113, and 115 to 125, reference is made to EP 1 144 623 B1.

5. Violation of Art. 100(c), Art. 123(2) EPC

The subject-matter of claim 1 and of independent claims 32, 63, 81, and 114 extends beyond the content of the European application, as originally filed, and therefore violate Article 123(2) EPC.

According to claim 1 "an oligonucleotide with double-stranded structure (dsRNA) formed by two separate RNA single strands is introduced in a cell in vitro, where one strand of the dsRNA has a region which is complementary to the target gene, characterized in that the complementary region has less than 25 successive nucleotide pairs".

The characterizing feature "the complementary region has less than 25 successive nucleotide pairs" has not been disclosed in the European patent application as originally filed. Therein, it is only disclosed that *"the region I, which is complementary to the target gene, has at most 49 successive nucleotide pairs"* (cf. WO

00/44895, p. 3, l. 5 to 7), but not less than 25 successive nucleotide pairs. Therefore, the subject-matter of claim 1 violates Article 123(2) EPC.

The above-mentioned feature which improperly broadens the scope of claim 1 is also a feature of independent claims 32, 63, 81, and 114. Therefore, the subject matter of independent claims 32, 63, 81, and 114 violates Article 123(2) EPC.

Consequently, the subject matter of dependent claims 2 to 31, 33 to 62, 64 to 80, 82 to 113, and 115 to 125 violates Article 123(2) EPC, because they depend directly or indirectly on the claims 1, 32, 63, 81, and 114.

Violation of Art. 123(2) EPC occurred on entry of the original PCT application into the regional phase before the EPO, when pages 1 to 8 of the description were amended on July 05, 2001

Enclosure RP1

and in new claims 1 to 125 were filed on August 08, 2001

Enclosure RP2

- compare **RP1**, form 1200.1, p. 2, item 6.2, and description, p. 3, l. l. 18, and p. 4, l. 11 to 18 amendments in handwriting; and compare **RP2**, amended claim 1, independent claims 32, 63, 81, and 124.

6. Lack of Novelty (Art. 100(a), Art. 54 EPC)

The subject matter of claim 1, independent claims 81 and 114, and dependent claims 4, 10, 11, 12, 14, 84, 90, 91, 92, 94, 115, 118, 120, 121, and 122 is not new over **D15**.

6.1 Missing Entitlement to Claim Priorities (Art. 89, Art. 54(2) (3) EPC)

The contested patent claims the priorities of January 30, 1999 (DE 19903713)

hereinafter: **P1**

and of November 11, 1999 (DE 19956568)

hereinafter: **P2**

The filing date of the European patent application, namely the filing date of the International patent application, is January 29, 2000

hereinafter: **FD**.

6.1.1 Granted claims 1 to 125 of the contested patent are not entitled to claim the priorities of **P1** and **P2**, because the claims 1 to 125 have been improperly extended, for reasons which have been discussed above (cf. item 5.).

6.1.2 In addition, claim 1 and dependent claims 2 to 31 are not entitled to claim the priority of **P1**.

The subject-matter of claim 1 refers to a *"Method for inhibiting the expression of a given target gene in a given cell in vitro"*.

However, no method for treating a cell in vitro has been disclosed in **P1** (DE 19903713), which only disclosed
"ein Medikament mit mindestens einem doppelsträngigen Oligoribonukleotid (dsRNA)" (**P1**, p. 2, l. 29 to 30),
use of dsRNA for the manufacture of a medicament *"Nach weiterer Maßgabe der Erfindung ist eine Verwendung doppelsträngiger Oligoribonukleotide zur Herstellung eines Medikaments zur Hemmung der Expression eines vorgegebenen Gens vorgesehen"* (**P1**, p. 4, l. 19 to 22), and
an example wherein the efficiency of transcription in the presence of dsRNA was determined in vitro in a cell-free system, using an commercially available cellular extract *"Testsystem mit menschlichem Zellkernextrakt: Unter Verwendung des HeLaScribe® Nuclear Extract in vitro Transkriptionskit's der Fa. Promega wurde die Transkriptionseffizienz des oben angegebenen Bereichs des "immediate early gene's" des Cytomegalievirus in Gegenwart der beiden einzelsträngigen Oligoribonukleotide sowie der dsRNA bestimmt."* (**P1**, p. 6, l. 18 to 23).

6.1.3 In addition, dependent claims 5, 36, 85, 116 and dependent claims 6 to 31, 37 to 61, 86 to 110, and 117 to 125 depending directly or indirectly on claims 5, 36, 85, and 116, respectively, are not entitled to claim priority **P1**.

Dependent claims 5, 36, 85, 116 comprise the feature *"where the target gene is selected from the following group: oncogene, cytokine gene, Id-protein gene, development gene, prion gene"*. However, no target gene selected from a cytokine gene, Id-protein gene, development gene, or prion gene has been disclosed in **P1**, which only disclosed *"die Therapie genetisch gesteuerter Krankheiten, z.B. Krebs und viraler Erkrankungen"* (**P1**, p. 4, l. 5 to 7).

6.1.4 In addition, dependent claims 12, 43, 67, 92 and dependent claims 13 to 31, 44 to 61, 68 to 80, and 93 to 113 depending directly or indirectly on claims 12, 43, 67, and 92, respectively, are not entitled to claim the priority of **P1**.

Dependent claims 12, 43, 67, 92 comprise the feature *"where the cohesion of the double-stranded structure, which is caused by the complementary nucleotide pairs, is increased by at least one, preferably two, further chemical linkage(s)"*. However, the **P1** discloses only *"... wobei die Enden der dsRNA zur Verhinderung eines Abbaus in der Zelle modifiziert sind"* (**P1**, claim 12, emphasis added). Therefore, the disclosure in **P1** does not support priority for the scope of the above-mentioned claims.

6.1.5 In addition, dependent claims 13, 14, 15, 19, 20, 21, 44, 45, 46, 50, 51, 52, 68, 69, 70, 74, 75, 76, 93, 94, 95, 99, 100, 101, and dependent claims 14 to 31, 45 to 61, 69 to 80, 94 to 113 refering directly or indirectly to one or more of the claims 13, 14, 15, 19, 20, 21, 44, 45, 46, 50, 51, 52, 68, 69, 70, 74, 75, 76, 93, 94, 95, 99, 100, 101, respectively, are not entitled to claim the priority of **P1**.

Dependent claims 13, 14, 15, 19, 20, 21, 44, 45, 46, 50, 51, 52, 68, 69, 70, 74, 75, 76, 93, 94, 95, 99, 100, 101 comprise several additional features of said chemical linkage(s) which have not been originally disclosed in **P1**, as has been stated above

for dependent claims 12, 43, 67, 92 (cf. above item 6.1.4.). For details of said additional features of the chemical linkage(s) it is referred to dependent claims 13, 14, 15, 19, 20, 21, 44, 45, 46, 50, 51, 52, 68, 69, 70, 74, 75, 76, 93, 94, 95, 99, 100, and 101.

6.1.6 In addition, dependent claims 16 to 18, 47 to 49, 71 to 73, 96 to 98 and dependent claims 17 to 31, 48 to 61, 72 to 80, 97 to 113, which depend directly or indirectly on one or more of the claims 16 to 18, 47 to 49, 71 to 73, 96 to 98, respectively, are not entitled to claim the priority of **P1** or **P2**.

Dependent claims 16 to 18, 47 to 49, 71 to 73, and 96 to 98 comprise the following features of chemical linkages (emphasis added):

"where the chemical linkage is formed by purine analogs used in the double-stranded structure in place of purines"

Claims 16, 47, 71, and 96

"where the chemical linkage is formed by azabenzene units introduced into the double-stranded structure"

Claims 17, 48, 72, 97

"where the chemical linkage is formed by branched nucleotide analogs used in the double-stranded structure in place of nucleotides"

Claims 18, 49, 73, 98

P1 does not disclose any of the particular chemical linkages claimed in dependent claims 16 to 18, 47 to 49, 71 to 73, and 96 to 98, but discloses only *"...wobei die Enden der dsRNA zur Verhinderung eines Abbaus in der Zelle modifiziert sind"* (**P1**, claim 12, emphasis added).

P2 discloses chemical linkages only within the complementary parts of the double stranded structure (**P2**, p. 6, l. 8 to 15), and discloses that the double-stranded structure can be longer than its part which is complementary to the target gene

"Die dsRNA kann also länger als der zum Zielgen komplementäre Bereich sein." (**P2**, p. 4, l. 12-14). Thus, **P2** does not disclose the subject matter of dependent claims 16 to 18, 47 to 49, 71 to 73, and 96 to 98.

6.1.7 In addition, dependent claims 22, 53, 77, 102 and dependent claims 23 to 31, 54 to 61, 78 to 80, 103 to 113 depending directly or indirectly on claims 22, 53, 77, 102, respectively, are not entitled to claim priority **P1** or **P2**.

P1 and **P2** do not disclose the subject-matter of dependent claims 22, 53, 77, and 102 that *"at least one 2'-hydroxyl group of the nucleotides of the dsRNA in the double-stranded structure is replaced by a chemical group, preferably a 2'-amino or a 2'-methyl group"*.

6.1.8 In addition, dependent claims 23, 54, 78, and 103 and dependent claims 24 to 31, 55 to 61, 79 to 80, and 104 to 113 depending directly or indirectly on claims 23, 54, 78, and 103, respectively, are not entitled to claim the priority of **P1** or **P2**.

P1 and **P2** do not disclose the subject-matter of dependent claims 23, 54, 78, and 103 that *"at least one nucleotide in at least one strand of the double-stranded structure is a locked nucleotide with a sugar ring which is chemically modified, preferably by a 2'-O, 4'-C-methylene bridge"*.

6.1.9 In addition, dependent claims 25, 26, 56, 57, 105, and 106 and dependent claims 27 to 31, 58 to 61, and 107 to 113 depending directly or indirectly on claims 25, 26, 56, 57, 105, and 106, respectively, are not entitled to claim the priority of **P1**.

P1 does not disclose the subject-matter of dependent claims 25, 56, and 105 that *"where the coat protein is derived from polyomavirus"*. Further, **P1** does not disclose the subject-matter of dependent claims 26, 57, and 106 that *"where the coat protein contains the polyomavirus protein 1 (VP1) and/or virus protein 2 (VP2)"*. **P1** only discloses that *"die dsRNA kann gleichfalls in virale natürliche Kapside oder in auf chemischem oder enzymatischem Weg hergestellte künstliche Kapside oder davon abgeleitete Strukturen eingeschlossen sein."* (**P1**, p. 3, l. 20 to 24).

6.1.10 In addition, dependent claims 27, 58, and 107 and dependent claims 28 to 31, 59 to 61, and 108 to 113 depending directly or indirectly on claims 27, 58, and 107, respectively, are not entitled to claim the priority of **P1**.

P1 does not disclose the subject-matter of dependent claims 27, 58, and 107 *"where, when a capsid or capsid-type structure is formed from the coat protein, one side faces the interior of the capsid or capsid-type structure"*.

6.1.11 In addition, dependent claims 28, 59, 79, 108, and 122 and dependent claims 29 to 31, 60, 61, 109 to 113, and 123 to 125 depending directly or indirectly on claims 28, 59, 79, 108, and 122, respectively, are not entitled to claim priority **P1**.

P1 does not disclose the subject-matter of dependent claims 28, 59, 79, 108, and 122 that *"where one strand of the dsRNA is complementary to the primary or processed RNA transcript of the target gene"*. In fact, **P1** does not even imply a mechanism of gene silencing, wherein the dsRNA of the alleged invention interferes with the mRNA of the target gene, because **P1** discloses: *"Der hemmende Effekt einzelsträngiger Antisinn-RNA wäre in diesem Testsystem nicht nachzuweisen, da hierbei die Inhibition auf der Ebene der Translation stattfindet. Hier wurde die Transkription untersucht."* (p. 7, l. 5 to 9).

6.1.12 In addition, dependent claims 29, 60, 109, and 123 and dependent claims 30, 31, 61, 110 to 113, 124, and 125 depending directly or indirectly on claims 29, 60, 109, and 123, respectively, are not entitled to claim the priority of **P1** as far as their subject-matter refers to *"where the cell is a vertebrate cell"*. **P1** only discloses *"es hat sich überraschend gezeigt, dass dsRNA sich als Medikament zur Hemmung der Expression eines vorgegebenen Gens in humanen Zellen eignet."* (DE 19903713, p. 2, l. 33 to p. 3, l. 2).

6.1.13 In addition, dependent claims 30, 61, 80, 110, and 124 and dependent claims 31, 62, 111, and 125 depending directly or indirectly on claims 30, 61, 80, 110, and 124 are not entitled to claim the priority of **P1** or **P2**.

P1 and **P2** do not disclose the subject-matter of dependent claims 30, 61, 80, 110, and 124 that *"where at least two dsRNAs which differ from each other are introduced into the cell, where at least segments of one strand of each dsRNA are complementary to in each case one of at least two different target genes"*.

6.1.14 In addition, dependent claims 31, 62, 111, and 125 are not entitled to claim the priority of **P1** or **P2**.

P1 and **P2** do not disclose the subject-matter of dependent claims 31, 62, 111, and 125 *"where one of the target genes is the PKR gene"*.

6.2 Missing Novelty of the Subject-Matter of Claim 1, Independent Claims 81 and 114, and of Dependent Claims 4, 10, 11, 12, 14, 84, 90, 91, 92, 94, 115, 118, 120, 121, and 122 over Prior Art Document D15

6.2.1 Claim 1 of the contested patent is not entitled to claim the priority of **P1** (cf. above item 6.1.2). Therefore, the subject-matter of claim 1 is not new over **D15**, which discloses:

1. Method for inhibiting the expression of a given target gene (**D15**, p. 2, l. 5 to 9 and p. 5, l. 14 to 20),
2. in a cell (**D15**, p. 2, l. 5 to 9 and p. 5),
3. in vitro (**D15**, p. 7, l. 7, disclosing cell cultures),
4. where an oligoribonucleotide is introduced into the cell (**D15**, p. 2, l. 6)
5. the oligoribunocleotide has a double-stranded structure (dsRNA) (**D15**, p. 2, l. 5 to 9 and p. 4, l. 17 to 20),
6. the dsRNA is formed by two separate RNA single strands (**D15**, p. 2, l. 10-11, p. 7, l. 29 to 31),
7. one strand of the dsRNA has a region which is complementary to the target gene (**D15**, p. 4, l. 17),

8. the complementary region has less than 25 successive nucleotide pairs (**D15**, p. 11, l. 22 to 23).

Therefore, the subject-matter of claim 1 is not new over **D15**.

6.2.2 Claim 1 of the contested patent is not entitled to claim the priority of **P1** (cf. above item 6.1.2). Therefore, the subject-matter of claim 1 is not new over **D14**, which discloses:

1. Method for inhibiting the expression of a given target gene (**D14**, p. 950, left column, l. 1),
2. in a cell in vitro (**D15**, p. 951, middle column, l. 7 to 11),
3. where an oligoribonucleotide is introduced into the cell, which has a double-stranded structure (dsRNA) (**D14**, p. 950, left column, l. 6 to 11),
4. the dsRNA is formed by two separate RNA single strands (**D14**, p. 950, Figure B and Figure C and legend to Figure 1),
7. one strand of the dsRNA has a region which is complementary to the target gene (**D14**, p. 950, Figure A, Figure B and Figure C and legend to Figure 1),
8. the complementary region has less than 25 successive nucleotide pairs (implizitly disclosed in **D14**, abstract, l. 5 to 6 *"These RNA molecules were of a uniform length, estimated at 25 nucleotides ..."* [emphasis added]; and on p. 951, left column, l. 1 to 3: *"As for PTGS of ACO in tomato, the GUS antisense RNA was a discrete species of about ~25 nt."* [emphasis added]).

Therefore, the subject-matter of claim 1 is not new over **D14**.

6.2.3 Dependent claim 4 of the contested patent is not entitled to claim the priority of **P1** (cf. above item 6.1.2). The subject-matter of dependent claim 4 is not new over **D15**, which discloses:

1. the method according to claim 1 (cf. above item 6.2.1),
2. the target gene is expressed in eukaryotic cells (**D15**, claim 1 of D15, wherein the RNA fragments are introduced into a plant cell).

Therefore, the subject-matter of dependent claim 4 is not new over D15.

6.2.4 Dependent claim 10 of the contested patent is not entitled to claim the priority of **P1** (cf. above item 6.1.2). The subject-matter of dependent claim 10 is not new over **D15**, which discloses:

1. the method according to claim 1 or 4 (cf. above items 6.2.1 and 6.2.3),
2. the segments of the dsRNA are in double-stranded form (**D15**, p. 1, l. 28 to 31; p. 11, l. 6 to 8; p. 12, l. 17 to 18).

Therefore, the subject-matter of dependent claim 10 is not new over **D15**.

6.2.5 Dependent claim 11 of the contested patent is not entitled to claim the priority of **P1** (cf. above item 6.1.2). The subject-matter of dependent claim 11 is not new over **D15**, which discloses:

1. the method according to claim 1, 4 or 10 (cf. above items 6.2.1 to 6.2.4),
2. the ends of the dsRNA are modified in order to counteract degradation in the cell (**D15**, p. 10, l. 12 to 13, which discloses the use of a transcriptional terminator for the stabilization of the transcribed RNA).

Therefore, the subject-matter of dependent claim 11 not new over **D15**.

6.2.6 Dependent claim 12 of the contested patent is not entitled to claim the priority of **P1** (cf. above item 6.1.2). The subject-matter of dependent claim 12 is not new over **D15**, which discloses:

1. the method according to claim 1, 4, 10 or 11 (cf. above items 6.2.1 to 6.2.5),
2. the cohesion of the double-stranded structure, which is caused by the complementary nucleotide pairs, is increased by at least one further chemical linkage (**D15**, p. 8, l. 9 to 10, which discloses a linker between the sense RNA fragment and the antisense RNA fragment of the RNA molecule).

Therefore, the subject-matter of dependent claim 12 is not new over **D15**.

6.2.7 Dependent claim 14 of the contested patent is not entitled to claim the priority of **P1** (cf. above item 6.1.2). The subject-matter of dependent claim 14 is not new over **D15**, which discloses:

1. the method according to claim 1, 4, 10, 11 or 14 (cf. above items 6.2.1 to 6.2.6),
2. the chemical linkage is generated at at least one end of the double-stranded structure (**D15**, p. 8, l. 9 to 10, which discloses a linker between the sense RNA fragment and the antisense RNA fragment of the RNA molecule).

Therefore, the subject-matter of dependent claim 14 is not new over **D15**.

6.2.8 The subject-matter of independent claim 81 of the contested patent is not new over **D15**, which discloses:

1. use of an oligoribonucleotide for preparing an active ingredient for inhibiting the expression of a given target gene (**D15**, p. 2, l. 6 to 11 and p. 5, l. 14 to 20, discloses a method of forming a double-stranded RNA molecule which can inhibit the expression of a target gene in a plant cell),
2. the oligoribonucleotide has a double-stranded structure (dsRNA) (**D15**, p. 2, l. 7 to 8),
3. the dsRNA is formed by two separate RNA single strands (**D15**, p. 2, l. 6 to 11),
4. one strand of the dsRNA has a region which is complementary to the target gene (**D15**, p. 4, l. 17 to 19, disclosing a sense RNA fragment of a target gene and an antisense RNA fragment of the same target gene, which both comprise nucleotide sequences complementary to one another),
5. the compelemtary region has less than 25 successive nucleotide pairs (**D15**, p. 11, l. 22 to 23).

Therefore, the subject-matter of independent claim 81 is not new over **D15**.

6.2.9 The subject-matter of dependent claim 84 of the contested patent is not new over **D15**, which discloses:

1. the use according to independent claim 81 (cf. above item 6.2.8),
2. the target gene is expressed in eukaryotic cells (**D15**, claim 1, comprising introducing RNA fragments into a plant cell).

Therefore, the subject-matter of dependent claim 84 is not new over **D15**.

6.2.10 The subject-matter of dependent claim 90 of the contested patent is not new over **D15**, which discloses:

1. the use according to independent claim 81 or dependent claim 84 (cf. above items 6.2.8 or 6.2.9),
2. segments of the dsRNA are in double-stranded form (**D15**, p. 1, l. 28 to 31; p. 11, l. 6 to 8; p. 12, l. 17 to 18).

Therefore, the subject-matter of dependent claim 90 is not new over **D15**.

6.2.11 The subject-matter of dependent claim 91 of the contested patent is not new over **D15**, which discloses:

1. the use according to independent claim 81 or dependent claims 84 or 90 (cf. above items 6.2.8 to 6.2.10),
2. the ends of the dsRNA are modified in order to counteract degradation in the cell (**D15**, p. 10, l. 12 to 13, which discloses the use of a transcriptional terminator for the stabilization of the RNA).

Therefore, the subject-matter of dependent claim 91 is not new over **D15**.

6.2.12 The subject-matter of dependent claim 92 of the contested patent is not new over **D15**, which discloses:

1. the use according to independent claim 81 or dependent claims 84, 90 or 91 (cf. above items 6.2.8 to 6.2.11),
2. the cohesion of the double-stranded structure, which is caused by the complementary nucleotide pairs, is increased by at least one further chemical linkage (**D15**, p. 8, l. 9 to 10, which discloses a linker between the sense RNA fragment and the antisense RNA fragment).

Therefore, the subject-matter of dependent claim 92 is not new over **D15**.

6.2.13 The subject-matter of dependent claim 94 of the contested patent is not new over **D15**, which discloses:

1. the use according to independent claim 81 or dependent claims 84, 90, 91 or 92 (cf. above items 6.2.8 to 6.2.12),
2. the chemical linkage is generated at least at one end of the double-stranded structure (**D15**, p. 8, l. 9 to 10).

Therefore, the subject-matter of dependent claim 94 is not new over **D15**.

6.2.14 The subject-matter of independent claim 114 of the contested patent is not new over **D15**, which discloses:

1. use of a vector for coding at least one oligoribonucleotide (**D15**, p. 12, l. 28 to 30; p. 13, l. 32 to 33),
2. the oligoribonucleotide is for preparing an active ingredient (**D15**, p. 2, l. 6 to 9),
3. the oligoribonucleotide has a double-stranded structure (dsRNA) (**D15**, p. 2, l. 7 to 8),
4. the dsRNA is formed by two separate RNA single strands (**D15**, p. 4, l. 17 to 20),
5. the oligoribonucleotide is for inhibiting the expression of a given target gene (**D15**, p. 2, l. 5 to 9, p. 5, l. 14 to 20),
6. one strand of the dsRNA has a region which is complementary to the target gene (**D15**, p. 4, l. 17 to 24),

7. the complementary region has less than 25 successive nucleotide pairs (**D15**, p. 11, l. 22 to 23).

Therefore, the subject-matter of independent claim 114 is not new over **D15**.

6.2.15 The subject-matter of dependent claim 115 of the contested patent is not new over **D15**, which discloses:

1. the use according to independent claim 114 (cf. above item 6.2.14),
2. the target gene can be expressed in eukaryotic cells (**D15**, claim 1, which discloseg introducing RNA fragments into a plant cell).

Therefore, the subject-matter of dependent claim 115 is not new over **D15**.

6.2.16 The subject-matter of dependent claim 118 of the contested patent is not new over **D15**, which discloses:

1. the use according to independent claim 114 or dependent claim 115 (cf. above items 6.2.14 or 6.2.15),
2. the target gene is part of a virus (**D15**, p. 31, l. 32 to 33, wherein a recombinant plant DNA virus is disclosed, which is used to produce the sense and antisense RNA fragments capable of forming a dsRNA, and p. 2, l. 6 to 8 disclosing that said sense and antisense RNA fragments are of the target gene).

Therefore, the subject-matter of dependent claim 118 is not new over **D15**.

6.2.17 The subject-matter of dependent claim 120 of the contested patent is not new over **D15**, which discloses:

1. the use according to independent claim 114 or dependent claim 115 or 118 (cf. above items 6.2.14 to 6.2.16),
2. the virus is a virus which is phytopathogenic (**D15**, p. 31, l. 32, disclosing a plant virus).

Therefore, the subject-matter of dependent claim 120 is not new over **D15**.

6.2.18 The subject-matter of dependent claim 121 of the contested patent is not new over **D15**, which discloses:

1. the use according to independent claim 114 or dependent claim 115, 118 or 120 (cf. above items 6.2.14 to 6.2.17),
2. segments of the dsRNA are in double-stranded form (**D15**, p. 1, l. 28 to 31; p. 11, l. 6 to 8; p. 12, l. 17 to 18).

Therefore, the subject-matter of dependent claim 121 is not new over **D15**.

6.2.19 The subject-matter of dependent claim 122 of the contested patent is not new over **D15**, which discloses:

1. the use according to independent claim 114 or dependent claim 115, 118, 120 or 121 (cf. above items 6.2.14 to 6.2.18),
2. one strand of the dsRNA is complementary to the primary or processed RNA transcript of the target gene (**D15**, p. 2, l. 6 to 7, disclosing a sense RNA fragment of a target gene and an antisense RNA fragment, which are capable of forming a dsRNA, i.e. the antisense RNA fragment is complementary to the primary or processed RNA transcript of the target gene).

Therefore, the subject-matter of dependent claim 122 is not new over **D15**.

7. Lack of Inventive Step (Art. 100(a), Art. 56 EPC)

The subject-matter of claims 1 to 125 of the contested patent does not involve an inventive step (Art. 100(a), Art. 56 EPC).

7.1 Lack of Inventive Step of the Subject-Matter of Claims 1 to 31

7.1.1 Lack of Inventive Step of Claim 1

7.1.1.1 Closest Prior Art Document

The closest prior art document for claim 1 is **D11**, which also refers to genetic inhibition of a target gene using double-stranded RNA and which discloses almost identically all features of claim 1.

D11 was published on July 01, 1999 and is prior art according to Art. 54(2) EPC to claim 1, which is not entitled to claim the priority of **P1**, because **P1** does not disclose quite the same method as the alleged invention for treating a cell (cf. above item 6.1.2).

D11 discloses (emphasis added):

1. a method for inhibiting the expression of a given target gene (**D11**, claim 1, l. 1),
2. in a cell (**D11**, claim 1, l. 1),
3. in vitro (**D11**, p. 7, l. 3),
4. where an oligoribonucleotide is introduced into the cell (**D11**, claim 1, l. 2),
5. the oligoribunocleotide has a double-stranded structure (dsRNA) (**D11**, claim 1, l. 3),
6. the dsRNA is formed by two separate RNA single strands (**D11**, p. 6, l. 19 to 21),
7. one strand of the dsRNA has a region which is complementary to the target gene (**D11**, claim 1, l. 3 to 4),
8. the compelemtary region has 25 successive nucleotide pairs (**D11**, p. 11, l. 27 to 28).

The difference between claim 1 of the contested patent and **D11** is, that **D11** does not disclose the method according to claim 1, wherein a complementary region with **less than 25 nucleotide** pairs is used. All other features are identical!

7.1.1.2 Objective Problem which is Solved by the Subject-Matter of Claim 1 of the Contested Patent

The technical effects of the difference between claim 1 and **D11** are that the shorter complementary region in the method according to claim 1 requires shorter oligoribonucleotides than in **D11**. Shorter oligoribonucleotides are cheaper to produce, which is obviously known to the skilled in the art.

The objective problem of the alleged invention according to claim 1 was therefore, to provide an improved method for inhibiting the expression of a target gene, in particular a method, wherein a dsRNA is used, that can be cheaper produced than the dsRNA according to **D11**.

7.1.1.3 The person skilled in the art easily arrived at the subject-matter of claim 1 of the contested patent by combining **D11** with **D1**, which discloses the lin-4S RNA, which inhibits the lin-14 gene and comprises only 22 nucleotides. **D1** discloses:

1. that the lin-14 gene of C. elegans is inhibited by the 22 nucleotidelin-4S RNA (**D1**, summary, l. 14 to 20; p. 850, left col., l. 23 to 25),
2. the 22 nucleotide lin-4S RNA is in part complementary to a sequence of about 23 to 25 nucleotides in the lin-14 mRNA (**D1**, p. 848, left col., l. 16 to 17; Fig. 8 with legend;),
3. that the lin-4S RNA inhibits the lin-14 gene by complementary base pairing (**D1**, p. 849, right col., l. 6 to 11; p. 850, left col., l. 1 to 6).

Thus, **D1** already discloses a method for inhibiting the expression of a target gene by base pairing with an oligoribonucleotide containing a complementary region that comprises less than 25 base pairs, and which is therefore cheaper to produce than the oligonucleotides according to **D11**. The problem of the alleged invention was therefore easily solved by combining **D11** with **D1** without undue burden and without any inventive skill.

The reason for the skilled person in the art to combine **D11** and **D1**, was that both documents refer to studies in C. elegans (**D11**, p. 22ff), which has been an important model organism in the technical field of the alleged invention (compare the inventors of **D11** to the authers of **D3**, **D4**, **D5**, **D7**, and **D13**, which are among the leading scientists in the field, and compare the model organism). An additional reason for combining the teachings of **D11** with **D1** was, that the small lin-4S RNA has been proposed in **D2** to be the regulator for the LIN-28 gene of C. elegans, as well (**D2**, title; p. 637, right column, l. last five lines).

Therefore, the subject-matter of claim 1 of the contested patent does not involve an inventive step.

7.1.1.4 In alternative, **D14** can be considered the closest prior art, which also refers to double-stranded RNA and small antisense RNA in posttranscriptional gene silencing in plants. **D14** discloses almost identically all features of claim 1.

D14 was published on October 29, 1999 and is prior art according to Art. 54(2) EPC to claim 1, which is not entitled to claim the priority of **P1**, because **P1** does not disclose quite the same method as the alleged invention for treating a cell (cf. above item 6.1.2).

D14 discloses (emphasis added):

1. a method for inhibiting the expression of a given target gene (**D14**, abstract, l. 1 and 2),
2. in a cell (**D14**, p. 950, left column, l. 1 to 8),
3. in vitro (**D14**, p. 951, middle column, l. 3 to11)
4. where an oligoribonucleotide is introduced into the cell (**D14**, p. 951, middle column, l. 6 to 11),
5. the oligoribunocleotide has a double-stranded structure (dsRNA) (**D14**, p. 950, left column, l. 6 to 8),
6. the dsRNA is formed by two separate RNA single strands (**D14**, p. 950, middle column, l. 21 to 24, and Fig. 1 with legend),

7. one strand of the dsRNA has a region which is complementary to the target gene (**D14**, Figure 1B and legend; p. 951, right column, l. 31 to 38),
8. the compelemtary region has a length estimated at 25 nucleotides (**D14**, abstract, l. 5 to 6).

The difference between claim 1 of the contested patent and **D14** is, that **D14** does not **explicitly** disclose the method according to claim 1, wherein a complementary region with **less than 25 nucleotide** pairs is used. However, D14 discloses that the small antisense RNA has an **estimated** length of 25 nucleotides. All other features are identical!

7.1.1.5 Objective Problem which is Solved by the Subject-Matter of Claim 1 of the Contested Patent

The technical effects of the difference between claim 1 and **D14** are that the shorter complementary region in the method according to claim 1 requires shorter oligoribonucleotides than in **D14**. Shorter oligoribonucleotides are cheaper to produce, which is obviously known to the skilled in the art.

The objective problem of the alleged invention according to claim 1 was therefore, to provide an improved method for inhibiting the expression of a target gene, in particular a method, wherein a dsRNA is used, that can be cheaper produced than the dsRNA according to **D14**.

The skilled person in the art easily arrived at the subject-matter of the alleged invention, because the length of 25 bp had only been estimated in **D14** (**D14**, abstract, l. 5 to 6), and it was obvious that the lower boundary for the length of the complementary region had to be near the observed length of 25 bp (**D14**, p. 951, right column, l. 31 to 38) and could be determined in the next experiments.

Therefore, the subject-matter of claim 1 of the contested patent does not involve an inventive step.

7.1.2 Lack of Inventive Step of Dependent Claims 2 to 31

The subject-matter of dependent claims 2 to 31 lack an inventive step, because the subject-matter of claim 1 does not involve an inventive step (cf. above item 7.1.1) and the additional features in the dependent claims cannot cure that deficiency because they are obvious features for a person skilled in the art.

7.1.2.1 Lack of Inventive Step of Dependent Claim 2

The subject-matter of dependent claim 2 differs from that of claim 1 only by the feature: *"where the dsRNA is enclosed by micellar structures, preferably by liposomes"*.

However, **D11**, which like the contested patent refers to genetic inhibition by double-stranded RNA, discloses (p. 14, l. 20 to 21): *"Other methods known in the art for introducing nucleic acids to cells may be used, such as lipid-mediated carrier transport"*.

Therefore, the subject-matter of dependent claim 2 was obvious to the skilled person in the art, who knows that the cellular membrane has a lipid bilayer structure and that lipid-mediated carrier transport comprises transport by micellar structures, in particular by liposomes.

7.1.2.2 Lack of Inventive Step of Dependent Claim 3

The subject-matter of dependent claim 3 differs from that of claim 1 only by the feature: *"where the dsRNA is enclosed by natural viral capsids or by chemically or enzymatically produced artificial capsids or structures derived therefrom"*.

However, **D11**, which like the contested patent refers to genetic inhibition by double-stranded RNA, discloses (p. 14, l. 18 to 20): *"A viral construct packaged into a viral particle would accomplish both efficient introduction of an expressed construct into the cell and transcription of RNA encoded by the expression construct"*.

The subject-matter of dependent claim 2, wherein the dsRNA is enclosed in natural or artificial viral capsids or structures derived therefrom does not involve an inventive step by the skilled person in the art who knew from **D11**, that expression constructs for the production of dsRNA can be introduced into a target cell packaged into a viral particle.

7.1.2.3 Lack of Inventive Step of Dependent Claim 4

The subject-matter of dependent claim 4 differs from that of claim 1 only by the feature: *"where the target gene is expressed in eukaryotic cells"*.

However, **D11**, which like the contested patent refers to genetic inhibition by double-stranded RNA, discloses an extended list of eukaryotic organisms which express the target gene (p. 12, l. 3 to p. 13, l. 7). Therefore the subject-matter of dependent claim 4 was obvious for the skilled person in the art.

7.1.2.4 Lack of Inventive Step of Dependent Claim 5

The subject-matter of dependent claim 5 differs from that of claim 1 only by the feature: *"where the target gene is selected from the following group: oncogene, cytokine gene, Id-protein gene, developmental gene, prion gene"*.

However, **D11**, which like the contested patent refers to genetic inhibition by double-stranded RNA, discloses (p. 14, l. 25 to 30): *"The present invention may be used to introduce RNA into a cell for the treatment or prevention of disease. dsRNA may be introduced into a cancerous cell or tumor and thereby inhibit gene expression of a gene required for maintainance of the carcinogenic/tumorigenic phenotype. To prevent a disease or other pathology, a target gene may be selected which is required for initiation or maintenance of the disease/pathology."* Examples of target genes which developmental genes , cytokine genes and oncogenes are listed on p. 16, l. 22 to p. 17, l. 8 of **D11**).

Because all target genes mentioned in claim 5 are required for initiation or maintenance of some disease or pathological condition, the subject-matter of dependent claim 5 is obvious for the skilled person in the art.

7.1.2.5 Lack of Inventive Step of Dependent Claim 6

The subject-matter of dependent claim 6 differs from that of claim 1 only by the feature: *"where the target gene is expressed in pathogenic organisms, preferably in plasmodia"*.

However, **D11**, which like the contested patent refers to genetic inhibition by double-stranded RNA, discloses (p. 6, l. 9 to 10): *"The target gene may be a gene derived from the cell, an endogenous gene, a transgene, or a gene of a pathogen which is present in the cell after infection thereof"*, and (p. 7, l. 3 to 4): *"The cell with the target gene may be derived from or contained in any organism (e.g. plant, animal, protozoan, virus, bacterium, or fungus)*.

Plasmodia are well known to be important pathogens for mammals. In particular, the person skilled in the art knows that Plasmodium vivax is the pathogen that causes malaria, which is still the predominant human infection disease world-wide. As the alleged invention provides no specific disclosure about the use of dsRNA for the inhibition of plasmodial genes, the subject-matter of dependent claim 6 is obvious for the skilled in the art.

7.1.2.6 Lack of Inventive Step of Dependent Claim 7

The subject-matter of dependent claim 7 differs from that of claim 1 only by the feature: *"where the target gene is part of a virus or viroid"*.

However, **D11**, which like the contested patent refers to genetic inhibition by double-stranded RNA, discloses (p. 6, l. 9 to 10): *"The target gene may be a gene derived from the cell, an endogenous gene, a transgene, or a gene of a pathogen which is present in the cell after infection thereof"*, and (p. 7, l. 3 to 4): *"The cell*

with the target gene may be derived from or contained in any organism (e.g. plant, animal, protozoan, virus, bacterium, or fungus).

The subject-matter of claim 7 wherein the target gene is part of a virus is obvious from **D11**.

The person skilled in the art knows, that viroids are virus-like plant pathogens, which consist of small circular RNA molecules and do not possess a protein capside (**D18**). The alleged invention does not provide any specific disclosure about the use of dsRNA for the inhibition of viroids. The mere mentioning of viroids in dependent claim 7 is only subject-matter that is obvious because of **D11**, which discloses viral target genes.

7.1.2.7 Lack of Inventive Step of Dependent Claim 8

The subject-matter of dependent claim 8 differs from that of claim 1 only by the feature: *"where the virus is a virus or viroid which is pathogenic for humans"*.

However, **D11**, which like the contested patent refers to genetic inhibition by double-stranded RNA, discloses (p. 6, l. 9 to 10): *"The target gene may be a gene derived from the cell, an endogenous gene, a transgene, or a gene of a pathogen which is present in the cell after infection thereof"*, and (p. 7, l. 3 to 4): *"The cell with the target gene may be derived from or contained in any organism (e.g. plant, animal, protozoan, virus, bacterium, or fungus).*

The subject-matter of claim 8 which refers to the viral target gene which is pathogenic to humans is obvious from **D11** which discloses viral target gens and the use of dsRNA for the inhibition of human disease genes (cf. above item 7.1.2.4).

The subject-matter of claim 8 which refers to the viroid target gene which is pathogenic to humans cannot be carried out by the person skilled in the art (cf. below item 8.2).

7.1.2.8 Lack of Inventive Step of Dependent Claim 9

The subject-matter of dependent claim 9 differs from that of claim 1 only by the feature: *"where the virus or viroid is a virus or viroid which is pathogenic for animals or phytopathogenic"*.

The subject-matter of claim 9 comprises the feature, that the virus is either pathogenic to animals or is a phytopathogenic virus or viroid (cf. **D18**, "Viroide").

However, **D11**, which like the contested patent refers to genetic inhibition by double-stranded RNA, discloses (p. 6, l. 9 to 10): *"The target gene may be a gene derived from the cell, an endogenous gene, a transgene, or a gene of a pathogen which is present in the cell after infection thereof"*, and (p. 7, l. 3 to 4): *"The cell with the target gene may be derived from or contained in any organism (e.g. plant, animal, protozoan, virus, bacterium, or fungus)*. Therefore the subject-matter of claim 9 which refers to an animal pathogenic virus is obvious.

In addition, **D11** discloses (p. 17, l. 9 to 10): *"The present invention could comprise a method for producing plants with reduced susceptibility to (...) infection by apathogen"*.

Therefore, the subject-matter of claim 9 which refers to the use of dsRNA for the inhibition of a phytopathogenic virus or viroid is obvious over **D11**.

7.1.2.9 Lack of Inventive Step of Dependent Claim 10

The subject-matter of dependent claim 10 differs from that of claim 1 only by the feature: *"where segments of the dsRNA are in double-stranded form"*.

However, **D1** discloses the lin-4S RNA, which comprises two segements of complementarity to its target lin-14S mRNA at its ends (**D1**, Fig. 8B and legend). Therefore, the subject-matter of dependent claim 10 is obvious over **D1**.

7.1.2.10 Lack of Inventive Step of Dependent Claim 11

The subject-matter of dependent claim 11 differs from that of claim 1 only by the feature: *"where the ends of the dsRNA are modified in order to counteract degradation in the cell or dissociation into single strands"*.

However, **D15**, which also refers to dsRNA-mediated regulation of gene expression in plants, discloses (p. 8, l. 9 to 10): *"In yet another embodiment, the RNA molecule comprises a linker between the sense fragment and the antisense fragment"*. In addition, **D15** discloses (p. 10, l. 12 to 13): *"Use of a transcriptional terminator may serve to stabilize the RNA transcribed"*.

Therefore, the subject-matter of independent claim 11 is obvious over **D15**.

7.1.2.11 Lack of Inventive Step of Dependent Claim 12

The subject-matter of dependent claim 12 differs from that of claim 1 only by the feature: *"where the cohesion of the double-stranded structure, which is caused by the complementary nucleotide pairs, is increased by at least one, preferably two, further chemical linkage(s)"*.

However, **D15**, which also refers to dsRNA-mediated regulation of gene expression in plants, discloses (p. 8, l. 9 to 10): *"In yet another embodiment, the RNA molecule comprises a linker between the sense fragment and the antisense fragment"*.

Therefore, the subject-matter of independent claim 12 is obvious over **D15**.

7.1.2.12 Lack of Inventive Step of Dependent Claims 13 to 21

The subject-matter of dependent claims 13 to 21 differs from that of claim 1 in that it comprises several obvious examples of the chemical linkage according to dependent claim 12 (cf. above item 7.1.2.11).

The subject-matter of dependent claims 13 to 21 is obvious over **D15**, which discloses (p. 8, l. 9 to 10): *"In yet another embodiment, the RNA molecule comprises a linker between the sense fragment and the antisense fragment"*, because the chemical linkages according to claims 13 to 21 only comprise the usual chemical linkages between paired polynucleotide strands which are the most familiar chemical linkages for the person skilled in the art.

7.1.2.13 Lack of Inventive Step of Dependent Claims 22 and 23

The subject-matter of dependent claims 22 and 23 differs from that of claim 1 in that it comprises two examples of the chemical modifications of at least one of amino sugars in at least one strand of the double-stranded structure. However, said chemical modifications are the most familiar modifications for the person skilled in the art.

7.1.2.14 Lack of Inventive Step of Dependent Claim 24

The subject-matter of dependent claim 24 differs from that of claim 1 only by the feature: *"where the dsRNA is bound to, associated with or surrounded by, at least one viral coat protein which originates from a virus, is derived therefrom or has been prepared synthetically"*.

However, **D11**, which like the contested patent refers to genetic inhibition by double-stranded RNA, discloses (p. 14, l. 18 to 20): *"A viral construct packaged into a viral particle would accomplish both efficient introduction of an expressed construct into the cell and transcription of RNA encoded by the expression construct."*.

The subject-matter of dependent claim 24, wherein the dsRNA is associated with or surrounded by at least one natural or artificial viral coat protein does not involve an inventive step by the skilled person in the art who knew from **D11**, that expres-

sion constructs for the production of dsRNA can be introduced into a target cell packaged into a viral particle.

7.1.2.15 Lack of Inventive Step of Dependent Claims 25 and 26

The subject-matter of dependent claims 25 and 26 differs from that of claim 1 only by the features: *"where the coat protein is derived from polyomavirus"* (dependent claim 25), *"where the coat protein contains polyomavirus virus protein 1 (VP1) and/or virus protein 2 (VP2)"* (dependent claim 26), or (dependent claim 27).

The subject-matter of dependent claims 25 and 26 which refer to polyomavirus coat proteins are obvious for the person skilled in the art who knows that polyomaviruses comprise in particular Human Papillomavirus (HPV) which is a highly infectuous human virus, whose protein coat or a suitable protein thereof is therefore very suitable for introducing the dsRNA of the alleged invention into its target cell.

7.1.2.16 Lack of Inventive Step of Dependent Claim 28

The subject-matter of dependent claim 28 differs from that of claim 1 only by the feature: *"where one strand of the dsRNA is complementary to the primary or processed RNA transcript of the target gene"*.

However, **D7**, which like the contested patent refers to genetic inhibition by double-stranded RNA, discloses (p. 15505, left column, last but three and four lines): *"Exogenous dsRNA causes early degradation of homologous mRNA and/or mRNA precursor molecules"*.

Therefore, the subject-matter of claim 28 is obvious over **D7** for the person skilled in the art who knows that mRNA precursor molecules are synonymous to unprocessed primary transcripts of eukaryotic genes which comprise introns and have to be spliced to generate the mRNA.

7.1.2.17 Lack of Inventive Step of Dependent Claim 29

The subject-matter of dependent claim 29 differs from that of claim 1 only by the feature: *"where the cell is avertebrate cell or a human cell"*.

D11 was published on July 01, 1999 and is prior art according to Art. 54(2) EPC to dependent claim 29, which is not entitled to claim the priority of **P1** (cf. above item 6.1.12).

However, **D11**, which like the contested patent refers to genetic inhibition by double-stranded RNA, discloses (p. 2, l. 2 to 4): *"A further class of applications is therapeutically based in which it would be valuable for a functioning organism (e.g., a human) to reduce or remove the amount of a specified gene product (or products)"*, and (p. 12, l. 3 and 5): *"The cell with the target gene may be derived from or contained in any organism. (...) the animal may be a vertebrate or invertebrate"*.

Therefore, the subject-matter of dependent claim 29 is obvious for the skilled person in the art.

7.1.2.18 Lack of Inventive Step of Dependent Claim 30

The subject-matter of dependent claim 30 differs from that of claim 1 by the features: *"where at least two dsRNAs which differ from each other are introduced into the cell, where at least segments of one strand of each dsRNA are complementary to in each case one of at least two different target genes"*.

The subject-matter of claim 30 is obvious for the skilled person in the art who knows that one dsRNA can be introduced into a cell. In addition the skilled person nows comparable situations in the field of life science, e.g. a double transformant which comprises two different exogenous plasmid vectors.

7.1.2.19 Lack of Inventive Step of Dependent Claim 31

The subject-matter of dependent claim 31 differs from that of claim 1 by the features: *"where one of the target genes is the PKR gene"*.

However, **D5**, which like the contested patent refers to double-stranded RNA as a mediator in sequence-specific genetic silencing, discloses (p. 258, left column, last but three line, to middle column, l. 3; and middle column, l. 13 to 18): *"Mammalian cells exhibit a global antiviral response to double-stranded RNA. In this response, the PKR protein kinase recognizes dsRNA and unlashes a vehement but somewhat non-specific response leading to general translational arrest"*, and *"Any gene-specific interference by dsRNA in PKR-proficient mammalian cells would be dependent on a transient lapse in the PKR response, or on a controlled level of dsRNA that was incapable of activating PKR"*.

The skilled person in the art knew from **D5** that dsRNA could not be used in mammals, unless the PKR gene was not inhibited first. It was obvious to use dsRNA to inhibit the PKR gene, in order to allow for inhibiting of a target gene using an additional dsRNA.

7.2 Lack of Inventive Step of the Subject-Matters of Claims 32 to 62

7.2.1 Lack of Inventive Step of Independent Claim 32

7.2.1.1 Closest Prior Art Document

The closest prior art document for independent claim 32 of the contested patent is **D8**, which also refers to genetic inhibition of a target gene using double-stranded RNA and which discloses almost all features of independent claim 32. **D8** disclosed:

1. dsRNA injected into adult C. elegans nematodes specifically blocks gene activity (**D8**, p. 1018, left column, l. 12 to 15),

2. antisense and sense RNAs were synthesized and annealed for the ftz and eve genes of Drosophila (**D8**, p. 1018, left column, l. 18 to 39),
3. the RNAs were complementary to contiguous cDNA sequences (**D8**, p. 1024, left column, l. 43 to 44).
4. the smallest dsRNA comprised a complementary region of at least 176 nucleotide pairs (**D8**, p. 1024, left column, l. 46, *"2405-2581 for ds-wg"*),
5. similar effects of dsRNA on gene activity in nematode and insect species (**D8**, p. 1023, left column, l. 16 to 18),
6. the hypothesis that dsRNA interference controls gene expression in vertebrates (**D8**, p. 1023, left column, l. 20 to 22).

The differences between independent claim 32 and **D8** are, that **D8** does not explicitly disclose a *"medicament"* and that **D8** does not disclose that *"the complementary region has less than 25 nucleotide pairs"*.

7.2.1.2 Objective Problem which is Solved by the Subject-Matter of Dependent Claim 32 of the Contested Patent

The technical difference between the subject-matter of independent claim 32 and **D8** is, that claim 32 provides a product for human or animal healthcare containing shorter oligoribonucleotides.

The objective problem of the alleged invention according to independent claim 32 was therefore, to provide a product for human or animal healthcare.

7.2.1.3 The person skilled in the art of development of medicaments, who is specialized on diseases which involve the expression of genes, has the general objective to develop medicaments for the regulation of genes, in particular for the specific inhibition of a given target gene.

The person skilled in the art easily arrived at the subject-matter of independent claim 32 of the contested patent by combining **D8** with **D1**, which discloses the 22

nucleotide lin-4S RNA, which inhibits the lin-14 gene by complementary base pairing. **D1** discloses:

1. the proposal that the lin-14 gene of C. elegans is inhibited by the 22 nucleotide-lin-4S RNA (**D1**, summary, l. 14 to 20; p. 850, left col., l. 23 to 25),
2. the 22 nucleotide lin-4S RNA is in part complementary to a sequence of about 23 to 25 nucleotides in the lin-14 mRNA (**D1**, p. 848, left col., l. 16 to 17; Fig. 8 with legend;),
3. the proposal that the lin-4S RNA inhibits the lin-14 gene by complementary base pairing (**D1**, p. 849, right col., l. 6 to 11; p. 850, left col., l. 1 to 6).

Thus, **D1** already discloses the inhibition of a target gene by base pairing with an oligoribonucleotide, wherein the complementary region comprises less than 25 base pairs. Thus, the person skilled in the art who had the general objective to develop medicaments for the repression of a target gene, easily arrived at the subject-matter of independent claim 32 by combining **D8** with **D1**without undue burden and without any inventive skill.

The reason to combine **D8** with **D1** was that **D8** mentions the hypothesis that dsRNA interference controls gene expression in vertebrates, which comprise domestic animals and particular humans, for which most medicaments are developed.

An additional reason for combining the teachings of **D8** with **D1** was, that **D2** had postulated that the small lin-4S RNA could be the regulator of the lin-28 gene, as well (**D2**, title; p. 637, right column, l. last five lines).

Therefore, the subject-matter of independent claim 32 of the contested patent does not involve an inventive step.

7.2.2 Lack of Inventive Step of Dependent Claims 33 to 62

The subject-matter of dependent claims 33 to 62 lack an inventive step, because the subject-matter of claim 32 does not involve an inventive step (cf. above item

7.2.1) and the additional features in the dependent claims cannot cure that deficiency because they are obvious features for a person skilled in the art.

7.2.2.1 For the lacking inventive step of the subject-matter of dependent claims 33 to 62, reference is made to the lacking inventive step of the subject-matter of dependent claims 2 to 31, respectively (cf. above items 7.1.2.1 to 7.1.2.18), because the medicament according to independent claim 32 with the additional features of claims 33 to 62 lacks an inventive step for the same reasons as the subject-matter of claim 1 in combination with claims 2 to 31.

7.3 Lack of Inventive Step of the Subject-Matters of Claims 63 to 80

7.3.1 Lack of Inventive Step of Independent Claim 63

7.3.1.1 Closest Prior Art Document

The closest prior art document for independent claim 63 of the contested patent is **D6**, which like independent claim 63 refers to the use of dsRNA for inhibiting the expression of a target gene which is part of a phytopathogenic virus and which discloses almost all features of independent claim 63. **D6** discloses:

1. transgenic plants which have been transformed with sense and/or antisense constructs derived from the protease gene (Pro, **D6**, p. 13959, right column, l. 9;) of potato virus Y (PVY, **D6**, p. 13959, right column, l. 10);
2. coexpression of sense and antisense Pro mRNAs was much more effective at inducing PVY immunity than by transforming plants with only Pro genes in the sense orientation or Pro genes in the antisense orientation (**D6**, p. 13961, right column, l. 21 to 25; p. 13963, left column, l. 10 to 15; p. 13959, right column, l. 15 and legend to Fig. 1, second sentence);

3. a model, wherein the transgenes transcribe both sense and antisense mRNA, which hybridize to form a duplex, which leads to virus immunity (**D6**, p. 13961, right column, l. 11 to 14; p. 13964, Fig. 7, and legend to Fig. 7, l. 1 to 10),
4. the hypothesis that the delivery of RNAs with the potential to form duplexes may be an important new strategy for virus resistance in transgenic plants (**D6**, p. 13964, lright column, l. 26 to 28).

The differences between independent claim 63 of the contested patent and **D6** are, that D6 does not disclose an active ingredient, and does not disclose that one strand of the dsRNA has a complementary region to the target gene, which comprises less than 25 successive nucleotide pairs.

7.3.1.2 Objective Problem which is Solved by the Subject-Matter of Dependent Claim 63 of the Contested Patent

The technical effects of the differences between the subject-matter of independent claim 63 and **D6** are, that claim 63 provides a product instead of the method of **D6**, and that shorter oligoribonucleotides are required for the dsRNA of claim 63.

The objective problem of the alleged invention according to independent claim 63 was therefore, to provide an improved dsRNA for the inhibition of phytopatiogenic viruses.

7.3.1.3 The person skilled in the art who is specialized on the protection of plants against viral infections easily arrived at the subject-matter of independent claim 63 by combining **D6** with **D1**, which discloses the 22 nucleotide lin-4S RNA, which inhibits the lin-14 gene by complementary base pairing without undue burden and without inventive skill. **D1** discloses:

1. the proposal that the lin-14 gene of C. elegans is inhibited by the 22 nucleotide-lin-4S RNA (**D1**, summary, l. 14 to 20; p. 850, left col., l. 23 to 25),

2. the 22 nucleotide lin-4S RNA is in part complementary to a sequence of about 23 to 25 nucleotides in the lin-14 mRNA (**D1**, p. 848, left col., l. 16 to 17; Fig. 8 with legend;),
3. the proposal that the lin-4S RNA inhibits the lin-14 gene by complementary base pairing (**D1**, p. 849, right col., l. 6 to 11; p. 850, left col., l. 1 to 6).

Thus, **D1** discloses already the inhibition of a target gene by base pairing with an oligoribonucleotide, wherein the complemtary region comprises less than 25 base pairs. Thus, the person skilled in the art who had the general objective to develop active ingredients for the protection of plants against viruses, easily arrived at the subject-matter of independent claim 32 by combining **D6** with **D1.**

An additional reason for combining the teachings of **D6** with **D1** was, that **D2** had proposed that the small lin-4S RNA could be the regulator of the lin-28 gene, as well (**D2**, title; p. 637, right column, l. last five lines).

Therefore, the subject-matter of independent claim 63 of the contested patent does not involve an inventive step.

7.3.2 Lack of Inventive Step of Dependent Claims 64 to 80

The subject-matter of dependent claims 64 to 80 lack an inventive step, because the subject-matter of claim 32 does not involve an inventive step (cf. above item 7.3.1) and the additional features in the dependent claims cannot cure that deficiency because they are obvious features for a person skilled in the art.

7.3.2.1 For the lacking inventive step of the subject-matter of dependent claims 64 to 80, reference is made to the lacking inventive step of the subject-matter of dependent claims 4, 10 to 23, 28, and 30, respectively (cf. above items 7.1.2.4, 7.1.2.9 to 7.1.2.13, 7,1.2.16, and 7.1.2.17), because the active agent according to independent claim 63 with the additional features of claims 64 to 80 lacks an inventive step for the same reasons as the subject-matter of claim 1 in combination with claims 4, 10 to 23, 28, and 30.

7.4 Lack of Inventive Step of the Subject-Matters of Claims 81 to 113

7.4.1 Lack of Inventive Step of Independent Claim 81

The subject-matter of independent claim 81 is directed to:

1. Use of an oligoribonucleotide with double-standed structure (dsRNA),
2. the dsRNA is formed by two separate RNA single strands,
3. the dsRNA is used for preparing the medicament according to independent claim 32, or
4. the dsRNA is used for preparing the active ingredient according to independent claim 63.

The subject-matter of independent claim 81 does not involve an inventive step, because the subject-matters of independent claims 32 and 63, which comprise the dsRNA, do not involve an inventive step (cf. above items 7.2 and 7.3). The subject-matter of independent claim 81, which refers to the use of the dsRNA to produce the subject-matters of independent claims 32 and 63 is identical to the subject-matters of independent calims 32 and 63.

Therefore, the subject-matter of independent calim 81 does not involve an inventive step.

7.4.2 Lack of Inventive Step of Dependent Claims 82 to 111

The subject-matter of dependent claims 82 to 113 lack an inventive step, because the subject-matter of claim 81 does not involve an inventive step (cf. above item 7.4.1) and the additional features in the dependent claims cannot cure that deficiency because they are obvious features for a person skilled in the art.

7.4.2.1 For the lacking inventive step of the subject-matter of dependent claims 82 to 113, reference is made to the lacking inventive step of the subject-matter of dependent claims 2 to 31, respectively (cf. above items 7.1.2.1 to 7.1.2.18), because the use according to independent claim 81 with the additional features of claims 64 to 80 lacks an inventive step for the same reasons as the subject-matter of claim 1 in combination with claims 2 to 31.

7.4.3 Lack of Inventive Step of Dependent Claim 112

The subject-matter of dependent claim 112 lacks an inventive step, because the subject-matter of claim 81 does not involve an inventive step (cf. above item 7.4.1) and the additional feature of claim 112 *"where the medicament is injectable into the bloodstream or into the interstitium of the organism to undergo therapy"* cannot cure that deficiency because it is an obvious features for a person skilled in the art.

Already **D3**, which also refers to genetic interference by double-stranded RNA, discloses microinjection of dsRNA into the gonads, i.e. into the interstitium, of adult C. elegans worms (**D3**, p. 809, Fig. 3, legend, l. 5 to 6). **D11**, which also refers to genetic inhibition by double-stranded RNA already disclosed (p. 7, .l. 9 to 12): *"The RNA may be directly introduced into the cell (i.e., intracellularly); or introduced extracellularly into a cavity, interstitial space, into the circulation of an organism"*.

Therefore, the subject-matter of dependent claim 112 was obvious to the person skilled in the art.

7.4.4 Lack of Inventive Step of Dependent Claim 113

The subject-matter of dependent claim 113 lacks an inventive step, because the subject-matter of claim 81 does not involve an inventive step (cf. above item 7.4.1) and the additional feature of claim 113 *"where the dsRNA is taken up into bacteria*

or microorganisms" cannot cure that deficiency because it is an obvious features for a person skilled in the art.

D10 already discloses that (abstract, l. 8 to 9): *"Escherichia coli bacteria expressing dsRNA"* which can confer specific genetic interference effects on larvae of C. elegans that feed on these bacteria. Therefore, the subject-matter of dependent claim 113 is obvious for the skilled person in the art.

Only for reasons of completeness, it is mentioned, that feature *"microorganisms"* of dependent claim 113 is usually understood by the person skilled in the art as beeing synonymous to "bacteria". However, it is pointed out, that the description part of the contested patent does not comprise the subject-matter of dependent claim 113. Therefore, there is no disclosure in addition to dependent claim 113, and the feature *"microorganisms"* of dependent claim 113 only comprises bacteria.

7.5 Lack of Inventive Step of the Subject-Matter of Claims 114 to 125

7.5.1 Lack of Inventive Step of Independent Claim 114

The subject-matter of independent claim 114 is directed to:

1. Use of a vector for coding at least one oligoribonucleotide with double-standed structure (dsRNA),
2. the dsRNA is formed by two separate RNA single strands,
3. the dsRNA is for preparing the medicament according to independent claim 32, or
4. the dsRNA is for preparing the active ingredient according to independent claim 63.

The subject-matter of independent claim 114 does not involve an inventive step, because the subject-matters of independent claims 32 and 63 do not involve an in-

ventive step (cf. above items 7.2 and 7.3), and the use of a vector for coding the dsRNA of the subject-matters of independent claims 32 and 63 does not involve an inventive step, either.

The closest prior art for the subject-matter of claim 114 which refers to the use of a vector for encoding the dsRNA for a medicament is again **D8**, which is also the closest prior art for independent claim 32 (cf. above item 7.2.1.1). **D8** also discloses that plasmids are used as the templates for RNA synthesis (**D8**, p. 1024, left31 to 32).

Therefore, the subject-matter of independent claim 114, does not involve an inventive step for the same reasons as the medicament according to independent claim 32 (cf. above item 7.2.1.3).

The closest prior art for the subject-matter of claim 114 which refers to the use of a vector for encoding a dsRNA for an active ingredient is **D6**, which is also the closest prior art for independent claim 63 (cf. above item 7.3.1.1). **D6** also discloses plasmids for tobacco and rice transformation, which encode the sense and antisense Pro mRNAs (**D6**, p. 13959, right column, l. 6 to 10).

Therefore, the subject-matter of independent claim 114 does not involve an inventive step for the same reason as the active ingredient according to independent claim 63 (cf. above item 7.3.1.3).

7.5.2 Lack of Inventive Step of Dependent Claims 115 to 125

The subject-matter of dependent claims 115 to 125 lack an inventive step, because the subject-matter of claim 114 does not involve an inventive step (cf. above item 7.5.1) and the additional features in the dependent claims cannot cure that deficiency because they are obvious features for a person skilled in the art.

7.5.2.1 For the lacking inventive step of the subject-matter of dependent claims 115 to 125, reference is made to the lacking inventive step of the subject-matter of de-

pendent claims 4 to 10, and 28 to 31, respectively (cf. above items 7.1.2.3 to 7.1.2.9, and 7.1.2.16 to 7.1.2.18), because the use of a vector for coding at least one oligoribonucleotide according to independent claim 114 with the additional features of claims 115 to 125 lacks an inventive step for the same reasons as the subject-matter of claim 1 in combination with claims 4 to 10, and 28 to 31.

8. Insufficient Disclosure (Art. 100(b), Art. 83 EPC)

8.1 Claims 1 to 125 Comprise Subject-Matter that Cannot Be Carried Out by the Person Skilled in the Art

Claim 1, independent claims 32, 63, 81, and 114 and the dependent claims of the contested patent all comprise the characterizing feature *"the complementary region has less than 25 successive nucleotide pairs"*, which comprises subject-matter that cannot be carried out by a person skilled in the art. Therefore, all claims 1 to 125 of the contested patent comprise subject-matter that cannot be carried out.

Cited document **D17** , which was published on March 31, 2000, discloses that double-stranded RNA directs sequence-specific degradation of mRNA by the cleavage of the mRNA. Cleavage occurs only within the region of identity with the dsRNA. Noticably, cleavage occurs only at sites which are 21 to 23 nucleotide apart. The same interval is observed for the dsRNA itself, suggesting that the 21 to 23 nucleotide fragments from the dsRNA are guiding mRNA cleavage (**D17**, p. 25, summary; p. 26, left column, l. 31 to 34, l. 43 to 45, l. 51 to 56).

Prior to the cleavage of the mRNA, the dsRNA with more than 500 bp in length is itself cleaved into small fragments of 21 to 23 (**D17**, p. 27, right column, l. 20 to 31). No other stable dsRNAs were detected (**D17**, p. 27, right column, l. 41 to 42)!

The current model for dsRNA-directed mRNA cleavage is therefore that dsRNA is first cleaved to 21 to 23 nt long fragments, which then pair with the mRNA and

lead to cleavage of the mRNA to fragments of corresponding lengths (**D17**, p. 30, right column, l. 51 to 61).

This model is at varience with the characterizing feature of all claims of the contested patent, which comprises dsRNA with a complementary region to the target gene having less than 25 successive nucleotide pairs, and thus comprises dsRNA with a complementary region less than 21 nucleotide pairs. Such dsRNAs, however, do not exist (**D17**, p. 27, right column, l. 41 to 42).

Furthermore, all claims encompass dsRNA with a complementary region to the target gene having e.g. 1, 2 or 3 successive nucleotide pairs, and thus comprises dsRNA which obviously cannot function in the required manner.

Therefore, claim 1, independent claim 32, 63, 81, and 114 and claims 2 to 31, 33 to 62, 63 to 80, 82 to 113, and 115 to 125, which depend on one or more of claim 1, independent claim 32, 63, 81, and 114 comprise subject-matter that cannot be carried out by a person skilled in the art.

8.2 Dependent Claim 8 Comprise Subject-Matter that Cannot Be Carried Out by the Person Skilled in the Art

The subject-matter of dependent claim 8 differs from that of claim 1 only by the feature: *"where the virus is a virus or viroid which is pathogenic for humans"*.

The subject-matter of claim 8 which refers to the viroid target gene which is pathogenic to humans cannot be carried out by the person skilled in the art, because viroids are only plant pathogens (cf **D18**, "Viroide").

8.3 The Subject-Matter of Dependent Claim 27 Cannot Be Carried Out

The subject-matter of dependent claim 27 differs from that of claim 1 by the features: *"where, when a capsid or capsid-type structure is formed from the coat protein, one side faces the interior of the capsid or capsid-type structure"*.

The subject-matter of dependent claim 27 cannot be carried out by the person skilled in the art, because it is unclear *"one side"* of what *"faces the interior"*. The description does not provide further disclosure.

8.4 Claims 1 to 30, 32 to 61, 63 to 110, and 112 to 124 Comprise Subject-Matter that Cannot Be Carried Out by the Person Skilled in the Art

D5, which like the contested patent refers to double-stranded RNA as a mediator in sequence-specific genetic silencing, discloses (p. 258, left column, last but three line, to middle column, l. 3; and middle column, l. 13 to 18): *"Mammalian cells exhibit a global antiviral response to double-stranded RNA. In this response, the PKR protein kinase recognizes dsRNA and unlashes a vehement but somewhat non-specific response leading to general translational arrest"*, and *"Any gene-specific interference by dsRNA in PKR-proficient mammalian cells would be dependent on a transient lapse in the PKR response, or on a controlled level of dsRNA that was incapable of activating PKR"*.

According to the teaching of **D5**, the subject-matter of the alleged invention can only be carried out in mammals, if the PKR gene has previously been silenced or, possibly, if very low amounts of dsRNA are used, because otherwise, the introduction of the dsRNA of the alleged invention into a mammalian cell would elicit said anti-dsRNA response, which has drastic consequences for the cell.

However, only the subject-matter of dependent claim 31, 62, 111, and 125, which comprises the feature: *"where one of the target genes is the PKR gene"* allows for

the inhibition of the PKR gene. Therefore, it follows from **D5**, that the subject-matter of claims 1 to 30, 32 to 61, 63 to 110, and 112 to 124 of the contested patent, which do not depend on dependent claim 31, 62, 111, and 125, cannot be carried out by the person skilled in the art, if dsRNA-mediated gene inhibition shall be used in a mammal.

9. Summary

1. The subject-matter of the claims of the contested patent extends beyond the application as filed, and therefore violates Art. 123(2)EPC.

2. The subject-matter of claim 1, dependent claims 4, 10, 11, 12, 14, independent claim 81, dependent claims 84, 90, 91, 92, 94, independent claim 114, and dependent claims 115, 118, 120, 121, and 122 is not new over prior art document **D15**. The subject-matter of claim 1 is not new over prior art document **D14**.

3. The subject-matter of the claims does not involve an inventive step over prior art documents **D1** or **D5** or **D6** or **D8** or **D11** or **D14** or **D15** alone or in combination.

4. The subject-matter of the claims of the contested patent violates Art. 83 EPC.

5. Therefore, the request to revoke the contested patent as a whole based on Art. 100(a), (b), and (c) EPC is well substantiated.

R Bösl

Dr. Raphael Bösl
European Patent Attorney

Enc
c/ Rosalind C. Lee et al. 1993, **Enclosure D1**
c/ Eric G. Moss et al 1997, **Enclosure D2**
c/ Andrew Fire et al. 1998, **Enclosure D3**
c/ Yang Shi, and Craig Mello 1998, **Enclosure D4**

c/ Mary K. Montgomery and Andrew Fire 1998, **Enclosure D5**
c/ Peter M. Waterhouse et al. 1998, **Enclosure D6**
c/ Mary K. Montgomery et al. 1998, **Enclosure D7**
c/ Jason R. Kennerdell and Richard W. Carthew 1998, **Enclosure D8**
c/ Phillip A. Sharp 1999, **Enclosure D9**
c/ Lisa Timmons and Andrew Fire 1998, **Enclosure D10**
c/ WO 99/32619, **Enclosure D11**
c/ Anna Wargelius et al. 1999, **Enclosure D12**
c/ Andrew Fire 1999, **Enclosure D13**
c/ Andrew J. Hamilton and David C. Baulcombe 1999, **Enclosure D14**
c/ WO 99/61631, **Enclosure D15**
c/ Tuschl T et al. 1999, **Enclosure D16**
c/ Phillip D. Zamore et al. 2000, **Enclosure D17**
c/ Lexikon der Biochemie, **Enclosure D18**
c/ Entry of regional phase of July 05, 2001 with amended pages 1 to 8 of the description, **Enclosure RP1**
c/ Entry of regional phase, new claims 1 to 125 of August 08, 2001, **Enclosure RP2**
c/ DE 19903713, **Enclosure P1**
c/ DE 19956568, **Enclosure P2**
c/ WO 00/044895, **Enclosure FD**
c/ double of this opposition and its enclosures for the proprietor of the opposed patent